RESEARCH ON HERITABLE DISORDERS OF CONNECTIVE TISSUE

RELEASE DATE: January 7, 2002

RFA: RFA-AR-02-006

PARTICIPATING INSTITUTES AND CENTERS (ICs):

National Institute of Arthritis and Musculoskeletal and Skin Diseases
(http://www.niams.nih.gov/)
National Heart, Lung, and Blood Institute
(http://www.nhlbi.nih.gov/)

Letter of Intent Receipt Date: February 21, 2002
Application Receipt Date: March 21, 2002

THIS RFA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. MODULAR INSTRUCTIONS MUST BE USED FOR RESEARCH GRANT APPLICATIONS UP TO $250,000 PER YEAR. MODULAR BUDGET INSTRUCTIONS ARE PROVIDED IN SECTION C OF THE PHS 398 http://grants.nih.gov/grants/funding/phs398/phs398.html.

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Heart, Lung, and Blood Institute (NHLBI) invite applications for basic and clinical research on heritable disorders of connective tissue. Heritable disorders of connective tissue are rare diseases caused by abnormalities in structural macromolecules and other molecules involved in their biosynthesis, processing, and degradation, regulatory molecules, cell membrane receptors and other molecules involved in signaling, and membrane transporters that reside wholly or partly in the extracellular matrix. A few hundred clinically defined conditions are gathered under this umbrella, and as many as 1 million people in the United States may have a heritable disorder of connective tissue. This announcement requests applications on mechanisms of disease pathogenesis and development of novel therapeutic strategies. Collaborative research, involving investigators with expertise in various scientific disciplines and clinical specialties is encouraged. The applications may be for individual research projects (R01) or for exploratory/developmental grants (R21). The objective of the exploratory/developmental mechanism (R21) is to encourage applications from individuals who are interested in testing

innovative or conceptually creative ideas that are scientifically sound and may advance our understanding of these disorders.

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to several objectives, particularly those listed in the chapter "Arthritis, Osteoporosis, and Chronic Back Conditions and Heart Diseases and Stroke." Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople/.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Faith-based organizations are eligible to apply for these grants. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

This RFA will use the R01 (investigator-initiated research project grant) and the R21 (exploratory/developmental research grant) award mechanisms. The R01 application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts being examined by the NIH. Complete and detailed instructions and information on Modular Grant applications can be found at http://grants.nih.gov/grants/funding/modular/modular.htm. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. Future unsolicited competing continuation applications will compete with all investigator-initiated applications and be reviewed according to the customary peer review procedures. The anticipated award date is September 30, 2002.

R21 Applications. Exploratory/developmental studies are not intended for large scale undertakings nor to support or supplement ongoing research. Instead, investigators are encouraged to explore the feasibility of an innovative research question or approach which may not be justifiable through existing research to compete as a standard research project grant (e.g., R01), and to develop a research basis for a subsequent application through other mechanisms, i.e., R01, P01.

Exploratory/developmental (R21) grants, may not exceed $75,000 per year in direct costs. The total project period for an R21 application submitted in response to this RFA may not exceed three years for the NIAMS and two years for the NHLBI. These grants are non-renewable and continuation of projects developed under the R21 program will be through the traditional unsolicited (R01 or P01) grant programs.

Investigators proposing to conduct small, pilot/toxicity clinical trials are advised to review the NIAMS and NHLBI guidelines for preparation of clinical trial applications and the NIAMS and NHLBI guidelines for Data and Safety Monitoring Boards http://www.nih.gov/niams.htm.

R01 Applications. Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the size of an award will vary also. Modular budgeting procedures apply for grants up to $250,000. Specific R01 application instructions have been modified to reflect "Modular grant" and "Just-in-time" streamlining efforts. For the NHLBI, the total project period must not exceed four years. Complete instructions and information on Modular Grants can be found at http://grants.nih.gov/grants/funding/modular/modular.htm.

FUNDS AVAILABLE

The estimated funds available for the first year of support for the program are $1,000,000 for NIAMS and $1,000,000 for NHLBI.

Because the nature and scope of the research proposed may vary, it is anticipated that the size of each award will also vary. Although the financial plans of the NIAMS and the NHLBI provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. At this time, it is not known if this RFA will be reissued.

RESEARCH OBJECTIVES

Background

Heritable disorders of connective tissue are rare diseases that result from abnormalities in many types of molecules, including structural macromolecules, enzymes involved in their biosynthesis, processing, and degradation, regulatory molecules like growth factors and transcription factors, cell membrane receptors and other molecules involved in signaling, and membrane transporters.

As a result, the number of disorders that can be considered to involve alterations in the structure, synthesis, degradation, or signaling pathways of molecules that reside wholly or partly in the extracellular matrix includes a few hundred clinically defined conditions. Some abnormalities may give rise to severe phenotypes, while others may produce milder symptoms. Examples of such diseases are Marfan's and Ehler-Danlos syndromes which can lead to life-threatening vasculopathies and intracardiac malformations.

In November, 2000, the NIAMS, the NIH Office of Rare Diseases, the March of Dimes, the Coalition for Heritable Disorders of Connective Tissue, and the Foundation for Basic Cutaneous Research sponsored the 3rd Workshop on Heritable Disorders of Connective Tissue at the NIH. The purpose of the workshop was to review current knowledge in this research area focusing on approaches to the question of pathogenesis of heritable disorders of connective tissue at all levels (genetic approaches, biochemical approaches, developmental approaches, and cell-matrix interactions). By focusing on multidisciplinary approaches and common themes, the goals were to stimulate new collaborations between researchers interested in different diseases and more rapid progress in this area. By focusing on pathogenesis of heritable disorders of connective tissue, the goal was to gain that additional knowledge, beyond the first step of identification of disease genes, required for the development of new therapies.

The Workshop participants voiced a high priority for the continued development of mouse models of human diseases with in-depth studies on mechanisms of disease pathogenesis and the development of new therapeutic agents. They also described the potential for the development of stem cell therapies and the development of prenatal and preimplantation gene screening. Some broad areas of recommended research directions include, but are not limited to:

o Pathogenesis of connective tissue using human and mouse models

o Identification of secondary mechanisms of pathogenesis

o Determinants of phenotypic variability in mice and humans; the role of stochastic variations in genotype-phenotype correlations

o Use of existing and development of new mouse models to understand pathological sequence of events and to develop therapies

o Development of in vitro approaches to fully exploit mouse models and test in vitro/in vivo correlations

o Hierarchy of the assembly and diversification of the extracellular matrix

o Quantitative determination of molecular interactions of matrix molecules

o Protein-protein interactions both inside and outside the cell

o Role of the extracellular matrix in tissue assembly and homeostasis; matrix assembly as a complex whole; regulators of matrix assembly

o Role of the ECM in morphogenesis and cell differentiation

o Development of therapies for connective tissue repair and regeneration

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the AMENDMENT "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.
The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the Inclusion of Children as Participants in Research Involving Human Subjects that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html.

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning these policies.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at: http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this RFA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

LETTER OF INTENT

Prospective applicants are asked to submit, by February 21, 2002, a letter of intent that includes a descriptive title of the proposed research; the name, address, and telephone number of the Principal Investigator; the identities of other key personnel and participating institutions; and the number and title of this RFA. Although a letter of intent is not required, is not binding, does not commit the sender to submit an application, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload. The letter of intent is to be sent (e-mail, fax or post) to Dr. Tommy Broadwater at the address listed under INQUIRIES.

APPLICATION PROCEDURES

The PHS 398 research grant application instructions and forms (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html must be used in applying for these grants. This version of the PHS 398 is available in an interactive, searchable format. For further assistance contact GrantsInfo, Telephone 301/435-0714, Email: GrantsInfo@nih.gov.

RESEARCH PLAN

The research plan is limited to 25 pages for R01s and 10 pages for R21 applications (exclusive of cited references). Applications that exceed the page limit will be returned without review. An appendix may be included in the application; however, the appendix is not to be used to circumvent the page limit of the research plan.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS

Applications requesting up to $250,000 per year in direct costs must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these

applications by limiting the level of budgetary detail. Applicants request direct costs in $25,000 modules.
Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html includes step-by-step guidance for preparing modular grants. Additional information on modular grants is available at http://grants.nih.gov/grants/funding/modular/modular.htm.

The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/label-bk.pdf.

Submit a signed, typewritten original of the application, including the Checklist, and three signed, photocopies, in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040 - MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express mail or courier service)
At the time of submission, two additional copies of the application must be sent to Dr. Tommy Broadwater at the address listed under INQUIRIES.

Applications must be received by the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review. The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an Introduction addressing the previous critique.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the NIH Center for Scientific Review and for responsiveness by NIAMS and NHLBI staff; those judged to be incomplete or not in the format specified in this RFA will be returned to the applicant without review. Those considered to be non-responsive will be returned without review.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by NIAMS in accordance with the review criteria stated below. As part of the initial merit review, a process will be used by the initial review group in which all applications will receive a written critique but only those applications deemed to have the highest scientific merit will be discussed, assigned a priority score, and receive a second level review by the National Advisory Councils of the NIAMS and the NHLBI.

Review Criteria

The five criteria to be used in the evaluation of grant applications are listed below. To put those criteria in context, the following information is contained in instructions to the peer reviewers.

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. The reviewers will comment on the following aspects of the application in their written critiques in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered by the reviewers in assigning the overall score weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have a major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

2. Approach. Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation. Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

4. Investigator. Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

5. Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

The reasonableness of the proposed budget and duration in relation to the proposed research

The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application

The personnel category will be reviewed for appropriate staffing based on the requested percent effort. The direct costs budget request will be reviewed for consistency with the proposed methods and specific aims. For modular grant applications, any budgetary adjustments recommended by the reviewers will be in $25,000 modules. The duration of support will be reviewed to determine if it is appropriate to ensure successful completion of the requested scope of the project.

Schedule

Letter of Intent Receipt Date: February 21, 2002
Application Receipt Date: March 21, 2002
Peer Review Date: TBA

Council Review: September, 2002
Earliest Anticipated Start Date: September 30, 2002

AWARD CRITERIA

Award criteria that will be used to make award decisions include:
o scientific merit (as determined by peer review)
o availability of funds
o programmatic priorities

INQUIRIES

Inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome. Direct inquiries regarding programmatic issues to:

Cartilage and Connective Tissue

Dr. Bernadette Tyree
45 Center Drive, Room 5AS-25H
Bethesda, MD 20892-6500
Telephone: (301) 594-5032
FAX: (301) 594-4543
Email: TyreeB@mail.nih.gov

Muscle Biology

Dr. Richard W. Lymn
45 Center Drive, Room 5AS-49E
Bethesda, MD 20892-6500
Telephone: (301) 594-5128
FAX: (301) 480-4543
Email: LymnR@mail.nih.gov

Skin Diseases

Dr. Alan N. Moshell
45 Center Drive, Room 5AS-25L

Bethesda, MD 20892-6500
Telephone: (301) 594-5017
FAX: (301) 480-4543
Email: MoshellA@mail.nih.gov

Bone Biology

Dr. William J. Sharrock
45 Center Drive, Room 5AS-37A
Bethesda, MD 20892-6500
Telephone: (301) 594-5055
FAX: (301) 480-4543
Email: SharrocW@mail.nih.gov

Cardiovascular Diseases

Dr. Stephen S. Goldman
Vascular Biology Research Program
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
Rockledge 2
6701 Rockledge Drive, MSC 7956
Bethesda, MD 20892-7956
Telephone: (30) 435-0560
FAX: (301) 480-2858
Email: goldmans@nhlbi.nih.gov

Direct review inquiries to:

Dr. Tommy Broadwater
Review Branch
45 Center Drive, Natcher Bldg. Rm. 5A25U
Bethesda, MD 20892-6500
Telephone: (301) 594-4953
FAX: (301) 480-4543
Email: broadwat@mail.nih.gov

Direct inquiries regarding fiscal matters to:

Melinda Nelson
Grants Management Officer
45 Center Drive, Natcher Bldg. Rm. 5A49F
Bethesda, MD 20892-6500
Telephone: (301) 594-3535
FAX: (301) 480-5450
Email: nelsonm@mail.nih.gov

Beckie Chamberlin
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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410), as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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